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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,360	01/05/2005	Julie Kay Bush	X-14884	5540

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EXAMINER	
QAZI, SABIHA NAIM	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/30/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/520,360	BUSH ET AL.	
	Examiner	Art Unit	
	Sabiha Qazi	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

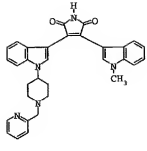
1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Final Office Action

Claims 2 and 15 are pending. Amendments are entered.

Summary of this Office Action dated April 12, 2008

1. 35 USC § 102 (b) Rejections
2. 35 USC § 103(a) --Rejections
3. Response to Remarks
4. Conclusion
5. Communication



The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 2 and 15 rejected under U.S.C. 102(b) as being anticipated by TEICHER et al[1]. See the entire document, especially lines 1-5 on page 9, lines 1-10 on page 7, lines 13-32, page 8, lines 27-31 on page 11, lines 20-30 n page 14, all examples, and claims especially claims 1, 3-7, 13.

TEICHER et al discloses the present compound, FB, in crystalline form and its salts, exemplified compound is dihydrochloride salts. The reference discloses the compound, compositions, and methods of treating neoplasm, and the combination with other anti-neoplastic agents.

Compound of formula 1 on page 7 is 3-[l- (1-(pyridin-2 methyl)piperidin-4-yl)-indol-3-yl]-4-(1 -methyhndol-3-yl)- 1H-pyrrole-2,5-dione or a pharmaceutically acceptable salt or solvate thereof (see lines 1-10 on page 7). **Monohydrocholide salt** of this compound is presently claimed.

[1] BEVERLY TEICHER et al; World Intellectual Property Organization Publication Number WO 02/02094 A2, published January 10, 2002.

It further discloses, "Because it contains a basic moiety, the compound of Formula I can also exist **as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric,** (lines 13-32, page 8).

Reference further discloses that the pharmaceutically acceptable salts of the compound of Formula I can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation **or crystallization**, or adventitious to such solvent. (see lines 1-5 in column 9).

In claim 2 the Applicant has cited the X-ray diffractions of their crystalline compound. However, since TEICHER et al discloses the crystalline forms of this compound and since the compound of prior art exists in crystalline form has the same utility and since no distinction has been made, claim 2 is considered anticipated by the prior art. The pharmaceutical composition will be the same as the prior art because the compound is the same.

The reference discloses the method treating neoplasm. The reference further discloses a method for increasing apoptotic effects in malignant cells and inhibiting the signal transduction of angiogenic factors in tumors.

Since there is no showing, teaching or comparative data that the prior art hydrochloride is not the same as presently claimed, the claims of the present invention is anticipated by the reference.

35 USC § 102 (b) 2nd Rejection

Claims 2 and 15 are rejected under 35 U.S.C. 102 (b) as being anticipated by HEATH et al[2]. See the entire document, especially Example 49 in col. 45 and 46, Examples 45 and 46 in col. 43 and 44, Formulas II and III in col. 3 and 4.

HEATH et al discloses the present compound, compositions, and methods of use. The reference discloses pharmaceutically acceptable salts such as hydrochloric salts.[3] The reference also discloses that the compounds are potent, beta-1 and beta-2 isozyme selective PKC inhibitors.

In claim 2 the Applicants have cited the X-ray diffractions of their crystalline compound. HEATH et al discloses the same compound. The pharmaceutical composition is also discloses by the reference.

The instant invention is anticipated by the prior art because applicant provide no evidence that the X-ray diffraction of their compound is different is different from prior art compound.

Applicants claim are drawn to a crystalline monohydrochloride salt and its composition wherein the reference teaches dihydrochloride salt of the same compound.

[2] WILLIAM F. HEATH, JR. et al; United States Patent No. 5,545,636, published August 13 1996. See the entire document, especially Example 49 in col. 45 and 46, Examples 45 and 46 in col. 43 and 44, Formulas II and II in col. 3 and 4, examples, abstract, and claims.
[3] See lines 35-67 in col. 10.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 2 and 15 rejected under 35 U.S.C. 102 (e) as being anticipated by HEATH ET al. (for the same reasons as cited above).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

35 USC § 103(a) --- First Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2 and 15 are rejected under 35 U.S.C. 103(a) as being obvious over TEICHER et al[4].

TEICHER et al teaches the compound of formula 1 on page 7 is 3-[l- (1-(pyridin-2 methyl)piperidin-4-yl)-indol-3-yl]-4-(1 -methyhndol-3-yl)- 1H-pyrrole-2,5-dione or a pharmaceutically acceptable salt or solvate thereof (see lines 1-10 on page 7). Monohydrocholide salt of this compound is presently claimed. It further teaches, "Because it contains a basic moiety, the compound of Formula I can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric acid (lines 13-32, page 8). Reference further teaches that the pharmaceutically acceptable salts of the compound of Formula I can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation **or crystallization**, or adventitious to such solvent. (see lines 1-5 in column 9). TEICHER et al teaches the present compound, FB, and its salts, especially dihydrochloride salts. The reference teaches the compound, compositions, and methods of treating neoplasm, and the combination with other antineoplastic agents.

However, it would have been obvious to one skilled in the art at the time of invention to prepare the crystalline pharmaceutically acceptable salts such as hydrochloride salts because the prior art TEICHER et al teaches the crystalline forms of this compound. The pharmaceutical composition and the method of using will be the same as the prior art because the compound is the same.

Applicant must provide additional evidence to establish why their compound should be considered non-obvious, in absence of additional evidence to contrary, applicant's evidence must be deemed insufficient.

The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., >*Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps.");< *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

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[4] BEVERLY TEICHER et al; World Intellectual Property Organization Publication Number WO 02/02094 A2, published January 10, 2002. See the entire document, especially lines 6-10 on page 9, lines 1-10 on page 7, lines 27-30 on page 11, all of pages 12-20, examples, and claims.

In absence of any criticality and/or unexpected results, the instant invention is considered *prima facie* obvious over the cited prior art.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

35 USC § 103(a) --- Second Rejection

Claims 2 and 15 are rejected under 35 U.S.C. 103(a) as being obvious over HEATH et al[5].

HEATH et al teaches the present compound, compositions, and methods of use. This compound is a protein kinase inhibitor. The reference teaches pharmaceutically acceptable salts such as hydrochloric salts.[6] The reference also teaches the compounds are potent, beta-1 and beta-2 isozyme selective PKC inhibitors.

Instant invention differs from the reference in having a narrower scope than the prior art.

In claims 2 the Applicants have cited the X-ray diffractions of their crystalline compound. However, since the compound are potent, beta-1 and beta-2 isozyme selective PKC inhibitors, one skilled in the art at the time of invention would have been motivated to prepare the crystalline acid addition salts pharmaceutically acceptable salts such as hydrochloride salts because HEATH et al teaches the crystalline forms of this compound. The pharmaceutical

[5] WILLIAM F. HEATH, JR. et al; United States Patent No. 5,545,636, published August 13 1996. See the entire document, especially Example 49 in col. 45 and 46, Examples 45 and 46 in col. 43 and 44, Formulas II and II in col. 3 and 4, examples, abstract, and claims.
[6] See lines 35-67 in col. 10.

composition and the method of using will be the same as the prior art because the compound is the same.

X-ray diffraction data presented in claim 2 is not a comparative data. Applicant has provided no data for distinguishing their invention with the prior art. Due to the teaching s of the prior art presently claimed invention is considered prima facie obvious to one skilled in the art. Applicant must provide additional evidence to establish why their compound should be considered non-obvious, in absence of additional evidence to contrary, applicant's evidence must be deemed insufficient.

In absence of any criticality and/or unexpected results, the instant invention is considered *prima facie* obvious over the cited prior art.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

Response to Remarks

Applicant's arguments were fully considered but are not found persuasive. The arguments about each rejection were discussed in detail in a telephonic interview on February 5, 2008. Examiner has already discussed the prior art and the rejections so this response will be summarized to main issues. Examiner notes, that previously finality of the rejection was withdrawn on Applicant's request.

Claim Rejections - 35 USC § 102

Claim 2 is drawn to a crystalline form of 3-[l- (1-(pyridin-2 methyl)piperidin-4-yl)-indol-3-yl]-4-(1 -methyhndol-3-yl)- 1H-pyrrole-2,5-dione monohydrochloride and claim 15 is drawn to its composition. Examiner notes, that the X-ray diffraction cited in claim 2 cites "comprising" so that other peaks may also be present or added. There is no showing that X-Ray diffraction as cited is different from the compound already disclosed by the prior art. The invention as claimed in inherently taught by the prior art. TEICHER does teach the compounds or its pharmaceutically acceptable salt or solvate thereof. See lines 27-31, on page 11 and lines 20-30 on page 14. Heath discloses examples 45, 46 in column 43 and 44 and example 49 in column 46 discloses crystalline compounds. The reference discloses that that the compounds can be in crystalline form, and its pharmaceutically acceptable salts which includes hydrochloric acid salts, see compounds of formula II, III and IV in column 3 and 4.

35 USC § 103(a)---Rejections

TEICHER et al teaches the compound of formula 1 on page 7 is 3-[l- (1-(pyridin-2 methyl)piperidin-4-yl)-indol-3-yl]-4-(1 -methyhndol-3-yl)- 1H-pyrrole-2,5-dione or a pharmaceutically acceptable salt or solvate thereof (see lines 1-10 on page 7). Crystalline monohydrocholide salt of this compound is presently claimed. It further teaches, "Because it contains a basic moiety, the compound of Formula I can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric acid (lines 13-32, page 8). Prior art further teaches that the pharmaceutically acceptable salts of the compound of Formula I can also exist as various

solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation **or crystallization**, or adventitious to such solvent. (see lines 1-5 in column 9).

TEICHER et al teaches the present compound, FB, and its salts, especially dihydrochloride salts. The reference teaches the compound, compositions, and methods of treating neoplasm, and the combination with other antineoplastic agents.

Applicant must provide additional evidence to establish why their compound should be considered non-obvious, in absence of additional evidence to contrary, applicant's evidence must be deemed insufficient.

The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps, comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts". See KSR Supreme Court of United States Decision (Decided April 30, 2007, KSR INTERNATIONAL CO. v. TELEFLEX INC. et al. No. 04-1350) where it states that (1) "However, the issue is not whether a person skilled in the art had the motivation to combine the electronic control with an adjustable pedal assembly, but whether a person skilled in the art had the motivation to attach the electronic control to the support bracket of pedal assembly.

Rejection over HEATH et al is maintained for the same reasons as cited above.

Applicants argue that courts have been consistent in stating that polymorphs are patentable subject matter. *In re Cofer* has been cited but has not been followed by Applicants. No difference has been disclosed for any unexpected data by Applicant's. Similarly the subject matter US 6,335,347 is not closely related to present invention.

All the rejections are maintained.

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day except Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sabiha Qazi/

Primary Examiner, Art Unit 1612